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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/653,114	05/24/96	FALCK-PEDERSEN	E	19603/233(CR

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EXAMINER	
SCHNIZER,R	
ART UNIT	**PAPER NUMBER**
1632	40

DATE MAILED: 08/14/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/653,114	Applicant(s) FALCK-PEDERSEN, ERIK S	
	Examiner Richard Schnizer	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,9 and 17-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,9 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

An amendment was received and entered as Paper No. 39 on 6/7/01. Claims 1, 3, 4, 9, and 17-20 remain pending and are under consideration in this Office Action.

Rejections Withdrawn

The rejections of claims 1 and 9 under 35 USC 101 and 102 are withdrawn in view of Applicant's amendment.

The rejection of claims 1, 9, 17, and 19 as anticipated by Saito is withdrawn in view of Applicant's arguments.

The rejection of claim 20 under 35 USC 103 is withdrawn in view of Applicant's arguments.

Claim Rejections - 35 USC § 103

Claims 1, 3, 4, 9, and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Kirshenbaum *et al.*, Quantin et al., or Stratford-Perricaudet *et al.;* in view of Huang *et al.*, Choi *et al.*, Keating *et al.*, and KabiGen.

The invention is an adenoviral expression vector comprising at least one gene insertion site, a heterologous promoter upstream of the insertion site, eukaryotic splice acceptor and donor signals positioned downstream of the promoter and upstream of the insertion site, and a polyadenylation signal downstream of the insertion site. The promoter may be the mouse CMV

early promoter. The polyadenylation signal may be the mouse beta-globin polyadenylation signal. A form of the vector containing a heterologous sequence inserted into the insertion site is claimed, as is a unicellular host transformed with the vector. Methods of producing a selected protein by culturing infected or transformed hosts with the claimed vectors are also claimed.

Kirshenbaum *et al.* disclose a plasmid vector having Ad5 sequences which, when cotransfected with a mutant Ad5 construct into 293 cells, can recombine to produce a replication-incompetent virus containing the plasmid expression cassette (entire document, *e.g.* Methods). The replication cassette contains the human CMV promoter, the lacZ gene and the SV40 polyadenylation signal sequence. Within the plasmid, the expression cassette is flanked by Ad5 sequences that read on the left end packaging and replication sequences and homologous recombination sequences recited in claim 1. Kirshenbaum *et al.* also disclose transfected host cells producing β-galactosidase. Quantin *et al.* and Stratford-Perricaudet *et al.* each disclose similar products and methods, only different promoter and polyadenylation sequences are used in the expression cassette. None of the above three references discloses an expression cassette containing a splice site between the promoter and the gene to be expressed, nor do they disclose the use of the murine CMV early promoter and murine β-globin polyadenylation signal sequences. Huang *et al.* teach that including a splice site in the 5' untranslated portion of the gene to be expressed resulted in a much higher level of gene expression in several cell lines, including 293 (entire document, e.g. Fig. 2). Furthermore, Choi *et al.* (abstract) teach that incorporation of a generic intron between the promoter and the gene of interest causes 5- to 300-fold increases in

transgene expression in mice. Keating *et al.* teach that the murine immediate early CMV promoter produces a high level of gene expression in transfected cells (Table 1, Fig. 1). The KabiGen disclosure teaches that polyadenylation sequences from rodent β-globin genes yield efficient RNA processing in transfected cells (p5, lines 10-15). KabiGen also discloses vectors which contain additional cloning sites for insertion of additional genes (Figures).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the expression cassette of Kirshenbaum *et al.*, Quantin *et al.*, or Stratford-Perricaudet *et al.*, by including the splice site of either Huang *et al.* or Choi *et al.*, the murine CMV promoter of Keating *et al.*, and the murine β-globin polyadenylation sequence suggested by KabiGen. One skilled in the art would have been motivated to use these components in the expression cassette, given their recognized value for promoting high level gene expression and given the expectation that each component would continue to function in its known and expected manner. Thus the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made.

With respect to claim 20, it is noted that Stratford-Perricaudet teaches a method delivering heterologous genes to an animal heart in vivo. It would have been obvious to one of ordinary skill in the art to use in the method of Stratford-Perricaudet the vector obtained through the combination of the references cited above. One would have been motivated to do given the reasonable expectation that the vector would give enhanced gene expression.

Thus the invention as a whole was *prima facie* obvious.

Response to Arguments

Applicant's arguments of record have been fully considered as they pertain to the preceding rejection, but they are not persuasive.

Applicant's arguments against this rejection have been addressed in Paper 26. Subsequent to Paper 26, Applicant submitted the declaration of Dr. Kovesdi (Paper No. 36, filed 5/30/00). This declaration was considered in Paper No. 38, and is given further consideration below.

Dr. Kovesdi argues that one of skill in the art at the time of the invention would have believed that the incorporation of an intron into an adenoviral vector would not result in enhanced expression, as has been shown to be the case in other vectors and in transgenes. Points 8-11 of the declaration are set forth in support of this position. These points will be considered in sequence as follows.

Point No.8 stresses that adenovirus is larger and more complex than other gene expression systems, that adenovirus encodes multiple alternatively spliced mRNAs, that adenoviruses require for their life cycles cellular factors that are not required by plasmid-based expression vectors, and that adenovirus is bound to the nuclear matrix and does not float free like a plasmid. In response, the Examiner points out that Applicant has provided no nexus between the efficiency of gene expression, as it is affected by introns, and any of these factors, and has provided no support for the contention that one of ordinary skill in the art would not have believed that an intron would function to increase expression in an adenoviral context. Furthermore, Applicant's argument with respect to the effect of the size and complexity of the vector is refuted by Choi, cited above, who

teaches that incorporation of a generic intron between the promoter and a gene of interest causes 5- to 300-fold increases in transgene expression in mice. The size and complexity of a mammalian chromosome vastly exceed that of an adenoviral genome.

Point No. 9 shows that promoter activity is unpredictable in the context of an adenoviral vector. However, Applicant has failed to provide a nexus between this point and the effect of introns on gene expression. For example, Applicant has provided no basis to believe that the introduction of an intron after any of the exemplified promoters would not enhance expression from these promoters.

In Point 10, Applicant notes that the adenoviral genome comprises numerous splice sites, and that much alternative splicing occurs in the course of adenoviral gene expression. However, Applicant has failed to establish why one of ordinary skill in the art would have expected this to affect the expression of a message from a heterologous transcription unit embedded in the adenovirus. There is no readily apparent reason to expect that expression from a heterologous promoter will be affected by alternative splicing of messages transcribed from unrelated promoters, and Applicant has failed to set forth any such reason.

Point 11 focuses on the tightly regulated control of adenoviral message splicing. Again, it is unclear why the splicing of authentic adenoviral messages would be expected to have any effect on the expression of a heterologous message expressed from an adenoviral platform. Applicant has provided no evidence that one of skill in the art at the time of the invention would have

expected an intron in a heterologous transcription unit located in an adenovirus to have any different effect than it does in a plasmid or chromosomal context.

Applicant's arguments depend on the notion that there is something about an adenovirus which would cause one of ordinary skill in the art to doubt that an intron in a heterologous transcription unit in an adenovirus would function differently than in any other context. The evidence of record shows that introns enhance gene expression in plasmids (Huang et al), in chromosomal transgenes (Choi et al), and in viruses (Buchman and Berg). At the time the invention was filed, the mechanism of this enhancement was thought to involve an increase in message stability due to an increase in the efficiency of polyadenylation. See Huang and Choi. Huang considered four possible explanations for the observed effect of introns on transcription of heterologous genes, and concluded that it was unlikely that the effect was due to transcription initiation or elongation. See page 945, column 2, first and second full paragraphs. In other words, the effect was post-transcriptional, and did not appear to involve the template in any way. This view is supported by Choi et al. See page 3073, column 2, lines 12-18 of first full paragraph. For this reason it is difficult to imagine why one of ordinary skill in the art would doubt that an intron would enhance expression of a heterologous gene from an adenoviral platform. If there is no effect at the level of expression which directly involves the template, why would the nature of the template, make any difference in expression? Applicant has present no evidence of arguments that suggest that one of ordinary skill in the art at the time of the invention would have expected that the transcription or splicing of authentic adenoviral messages should affect the post-

transcriptional processing of a heterologous mRNA expressed from an adenoviral platform in any way.

For these reasons, the rejection is maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 103-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Patsy Zimmerman whose telephone number is 703-308-8338.

Deborah Crouch

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Richard Schnizer, Ph.D.